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Citation for published version:

Fearon, KCH & Baracos, VE 2010, 'Cachexia in pancreatic cancer: new treatment options and measures of success' HPB, vol. 12, no. 5, pp. 323-4. DOI: 10.1111/j.1477-2574.2010.00178.x

Digital Object Identifier (DOI):

[10.1111/j.1477-2574.2010.00178.x](https://doi.org/10.1111/j.1477-2574.2010.00178.x)

Link:

[Link to publication record in Edinburgh Research Explorer](#)

Document Version:

Publisher's PDF, also known as Version of record

Published In:

HPB

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EDITORIAL

Cachexia in pancreatic cancer: new treatment options and measures of success

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Cachexia has long been recognized as a direct cause of reduced quality of life complicating both the early and late stages of cancer, particularly in patients with tumours originating in the pancreas, oesophagus, stomach or lung. Weight loss in cancer can result from reduced food intake or abnormal metabolism or, most commonly, a variable combination of the two. These changes are induced by changes in the neuro-endocrine stress response and activation of pro-inflammatory cytokine networks. Loss of adipose tissue (reflecting a negative energy balance) and wasting of skeletal muscle (reflecting a negative nitrogen balance) may or may not develop in synchrony. Hepatic protein synthesis is activated with development of an acute phase protein response. Central nervous system (CNS) changes include anorexia and fatigue. Taken together, these changes are thought to contribute to the reduced quality and quantity of life associated with cachexia.

Patients with pancreatic cancer have the highest prevalence and often develop the most severe degrees of cachexia.¹ Traditional understanding of cachexia has focused on loss of body weight. However, a number of specific methods currently available to discriminate detailed body composition have recently indicated that skeletal muscle and adipose tissue may behave independently during weight loss. Skeletal muscle wasting is a phenomenon which, without the aid of body composition analysis, may be obscured within the bulk of body fat and it has only recently been recognized that *sarcopenia* (severe muscle loss to an absolute level >2 standard deviations below that typical of healthy adults) is a clinically important phenomenon, even in overweight or obese patients. The ageing process is often paralleled by decreases in muscle and increases in fat mass, which may culminate in *sarcopenic obesity*. Current literature on human body composition is becoming highly differentiated and, although this is most developed in studies of non-malignant conditions such as old age, diabetes and obesity, current research on cancer cachexia is increasingly employing such techniques to reveal the true scale of sarcopenia in both obese and non-obese patients.

The present study by Aslani and co-workers² examines the relationship between tumour stage and altered body composition in patients with resectable pancreatic cancer. The methods employed include total body potassium counting, assessment of total body water and estimation of fat mass by anthropometry (skin-fold thickness). These methods allow for the separation of compartments (fat, protein, water), but not specific subsets within them (i.e. muscle vs. organs) and are dependent on the availability of the highly specialized equipment necessary for potassium measurement. Other recent works on pancreatic cancer cachexia^{3,4} have made opportunistic use of the computed tomography (CT) images found in the usual patient record, which allow the separation of specific muscles and organs, as well as visceral, subcutaneous and intermuscular adipose tissues. Both CT and magnetic resonance imaging (MRI)-based approaches have been validated extensively in non-malignant and, more recently, malignant disease.^{5,6}

In the study by Aslani *et al.*,² patients with more advanced disease (involved surgical margins) are shown to have more significant alterations in body composition, notably decreased body protein mass and fat mass. The sample size was small and patients were examined whilst their disease was still resectable. It remains to be seen whether these early changes predict the later degree and impact of cachexia on outcome. Interestingly, the presence of muscle wasting in obese patients with advanced pancreatic cancer is associated with shortened survival.³

One of the key domains of quality of life that is affected by cachexia is thought to be physical function.⁷ New technology (physical activity monitors) provide a robust, objective measure of this variable and such monitoring has been suggested as a novel and important endpoint for cachexia intervention trials.⁸ Physical activity level is grossly decreased in advanced cancer patients with weight loss and may be influenced beneficially by specialized nutritional support.⁹ There is, however, little clear information on the relative importance of altered energy supply, reduced muscle mass, systemic inflammation or CNS/psychological alterations

(e.g. fatigue) on physical activity level. Such issues might be resolved by the development of effective therapy for cachexia and concomitant use of activity monitoring in proof-of-concept trials.

Recent advances in molecular and cell biology have provided a range of novel drug targets relevant to the treatment of cachexia. Interventions may be either upstream (e.g. by antagonizing key mediators of systemic inflammation) or downstream (e.g. by blocking catabolic pathways or stimulating anabolic pathways in skeletal muscle). Upstream targets have the advantage of affecting multiple aspects of cachexia. For example, interleukin-6 is known to be the main mediator of the hepatic acute phase response in humans, but it may also play a role in anorexia, fatigue, anaemia, oedema and muscle loss. By contrast, myostatin acts as a physiological brake to the continued growth of skeletal muscle and is therefore a potential downstream target. The blockade of myostatin offers a specific method to induce muscle hypertrophy independent of the provision of anabolic signals (e.g. insulin-like growth factor, IGF-1) which, at least theoretically, might stimulate cancer growth. Alternative targets include the melanocortin pathway in the CNS control of appetite. A powerful stimulus to increase food intake would potentially improve the mass and function of many organs and physiological functions. Therapies based on these pathways are currently in Phase I and Phase II clinical trials in cancer patients, and the demonstration of their potential efficacy to stem losses of weight and muscle, alter physical function and improve quality of life will be available in the foreseeable future.

Clearly, the best way to treat cachexia is to remove the tumour, as was investigated by Aslani *et al.*² However, for the majority of patients with pancreatic cancer, resection is not possible and palliation with systemic chemotherapy is the main method of prolonging, albeit limited, survival. The balance between potential improved survival and maintenance of quality of life during chemotherapy is a key feature of management at this stage. Cachexia is associated with lower tolerance for chemotherapy, which limits the total dose that can be delivered, the number of symptomatic responses and any survival advantage that might be accrued.^{10–12} Moreover, for the majority who do not respond, cachexia may be exacerbated by systemic chemotherapy, thus increasing the net symptom burden experienced by patients.

It is now widely recognized that cachexia is best managed with a multimodal approach.¹³ Although specialized nutritional supplements are associated with weight stabilization, the effects are limited, which has reduced the enthusiasm of oncologists to actively pursue such anti-cachexia treatment strategies. It is now possible to make routine accurate measurements of key outcomes in cancer cachexia (namely, muscle mass and physical activity). The arrival of new potent strategies that may effectively reverse

such aspects of cachexia and support patients through palliative management (including chemotherapy) may herald a new era in which cachexia and its treatment are seen as essential components of mainline oncology.

Conflicts of interest

None declared.

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